

## Can the neutrophil/lymphocyte ratio be used to predict postoperative nausea and vomiting in children?

Neutrophil/lymphocyte ratio be used to predict postoperative nausea and vomiting

Sinan Yılmaz, Selda Şen  
Department of Anaesthesiology and Reanimation, Aydın Adnan Menderes University School of Medicine, Aydın, Turkey

### Abstract

**Aim:** The most important and most frequent complications after adenoidectomy (AE) or adenotonsillectomy (ATE) procedures in children are postoperative nausea and vomiting (PONV), and pain (POP). However, the implication of preoperative inflammation in these complications is still not clear. This study aimed to investigate whether the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) measured prior to the surgery would offer value in predicting the symptoms. **Material and Method:** The study included 127 children (2-10 years) who underwent elective adenoidectomy and adenotonsillectomy under general anesthesia. The patients were divided into two groups as adenoidectomy (AE, n=73) and adenotonsillectomy (ATE, n=54). The NLR and PLR were calculated in all patients. And also, intraoperative hemodynamic values, PONV, and POP were evaluated. **Results:** The rate of vomiting at any time post-surgery was 23.6% (n = 30) in all children. No significant difference was found between the groups (19.2% vs. 29.6%). Median NLR and PLR were 1.31 and 97.96 in the AE group, and 1.08 and 103.70 in the ATE group, respectively. Again, there was no difference between the two groups. Also, no correlation existed between the measurements of NLR or PLR and the PONV or POP. **Discussion:** The preoperative measures of NLR and PLR appear to be ineffective in predicting PONV or POP in children undergoing adenoidectomy or adenotonsillectomy.

### Keywords

Neutrophil-to-Lymphocyte Ratio; Platelet-to-Lymphocyte Ratio; Postoperative Vomiting; Children; Adenoidectomy; Adenotonsillectomy

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Corresponding Author: Sinan Yılmaz, Department of Anaesthesiology and Reanimation, Aydın Adnan Menderes University, School of Medicine, 09100, Aytepe, Aydın, Turkey. T.: +90 2564441256/2109 GSM: +905055954374 F.: +90 2562136064 E-Mail: dr\_snnylmz@hotmail.com  
ORCID ID: <https://orcid.org/0000-0002-5281-137X>

Introduction

Adenoidectomy and/or adenotonsillectomy are common surgical procedures for the treatment of recurrent throat infections and/or obstructive sleep apnea syndrome in children [1-2]. The most important and most frequent complications after these surgical procedures are postoperative nausea and vomiting (PONV) and pain (POP) [3]. POP is usually associated with the surgical procedure. Surgical trauma caused by incision, dissection, nerve stretching, and nerve compression causes inflammation and contributes to POP. However, the pathogenesis of PONV is a complex and known to result from ischemic, metabolic, neurogenic, pharmacological, or mechanical factors [3]. PONV and POP lead to prolonged hospitalization as well as to disturbance of the patient comfort [4].

The Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are widely used as markers of systemic inflammation in many diseases [5-6]. There is an increase in systemic inflammation markers and lymphoid tissue hypertrophy in children with adenoid and tonsil hypertrophy. Neutrophils and lymphocytes are the primary cells in the defense mechanism against infections [7]. Increased neutrophil and decreased lymphocyte counts during infections are important in the clinic [8]. The facts that analysis of cytokines, which have a critical role in the immune system, is expensive and that the cells from which they are secreted are not fully known limit their routine use in the diagnosis of infection. The NLR and PLR are widely used in the clinic since they are easy and inexpensive to determine and are related to inflammation [9-10]. The NLR and PLR have been previously studied especially in cardiac, vascular, and oncological diseases. However, to the authors' knowledge, no previous study has investigated the relationship between PONV or POP and NLR or PLR before, which are included in the preoperative assessment of children.

We hypothesized that preoperative NLR and PLR in children undergoing adenoidectomy or adenotonsillectomy could predict the likelihood of PONV or POP.

Material and Method

The study included 127 children (2-10 years) who underwent elective adenoidectomy and adenotonsillectomy under general anesthesia according to the American Society of Anesthesiology (ASA) I-II guidelines between February 1, 2018 and June 30, 2018. The local University ethics committee approved the study (Approval#: 2018/1310). An informed consent form was taken from the parents of each patient. In the power analysis based on the study of Elbistanlı et al. [11], it was established that at least 19 patients should be studied in each group to carry out a study with effect size 1.2, alpha 0.01, and statistical power 90% for NLR. The study was conducted prospectively and was registered with ClinicalTrials.gov. (NCT 03756909).

Children who had been taking antiemetic, opioid, or immunosuppressive treatment and those who had drug hypersensitivity, neurological disease, gastroesophageal reflux, obesity, immunodeficiency, or hematological disorders were excluded from the study. A questionnaire probing the history of nausea-vomiting, risk factors and family history of PONV was administered to all participants. Children with complete blood count performed one day before the surgery, were included in the study. Blood

samples were collected from the antecubital vein into tubes containing ethylene diamine tetraacetic acid (EDTA). Complete blood count was done with Mindray BC6800 hematology analyzer (MindrayInc., China). The NLR and PLR were obtained from neutrophil, lymphocyte, and platelet counts.

All patients were administered with 0.3 mg/kg oral midazolam 30 min before induction of general anesthesia. In the operating room, after routine monitoring, the general anesthesia was induced with 8% sevoflurane in 100% oxygen through a facemask with spontaneous ventilation. Before tracheal intubation, all patients were treated with 1µg/kg fentanyl and 0.6 mg/kg rocuronium. Afterward, anesthesia was maintained with 40% mixture of oxygen/nitrous oxide with 2% sevoflurane. The patients were divided into two groups as adenoidectomy (AE, n=73) and adenotonsillectomy (ATE, n=54). Six children who underwent tonsillectomy only were excluded from the study. All children were given 10 mg/kg intravenous paracetamol administered for postoperative analgesia.

All patients were routinely monitored in the operating room. Hemodynamic data including systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR) were monitored before entering the operating room (baseline), 5 min after the start of anesthesia, and at 15 min intervals during the first 60 minutes of surgery. Fasting period and the drugs and fluids applied during the operation were recorded from the anesthesia form.

The residual neuromuscular blockade was reversed with a mixture of neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. The infusion of 0.9% NaCl solution was stopped after tracheal extubation, and the patients were transferred to the post-anesthesia care unit (PACU). The evaluation of PONV was performed for all patients using a four-point scale: (0) no nausea/vomiting, (1) mild nausea/vomit, patient not requesting metoclopramide, (2) nausea/vomiting (patient requesting metoclopramide), and (3) nausea/vomiting resistant to metoclopramide [12]. All children's retching efforts (nausea and/or vomiting) were recorded at minutes as 1, 15, and 30 in PACU and hours as 1, 4, and 6 at the inpatient service. Postoperative vomiting was considered positive for a patient who vomited in any time period. The patients were evaluated for postoperative complications in PACU. Trained PACU nurses assessed pain severity according to the Children's Hospital East Ontario Pain Scale (CHEOPS) (Table 1) [13]. The CHEOPS scores were recorded at minutes as 1, 15, and 30 in PACU and hours 1, 4, and 6 at the inpatient service. Meperidine 1 mg/kg was administered when the CHEOPS score was ≥8. In the patients without any complications, oral intake was allowed 6 hours after surgery.

Table 1. Modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

| Score  | 0                  | 1                       | 2                          |
|--------|--------------------|-------------------------|----------------------------|
| Cry    | No cry             | Crying, moaning         | Scream                     |
| Facial | Smiling            | Neutral                 | Grimace                    |
| Verbal | Positive statement | Negative statement      | Suffering from pain        |
| Torso  | Neutral            | Variable, taot, upright | Stretched                  |
| Legs   | Neutral            | Kicking                 | Stretched, continuous move |

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of numeric variables. For all of the numeric variables that were not normally distributed, the comparison of two groups was done by the Mann-Whitney U test and descriptive statistics were presented as median (interquartile range (IQR)). The Chi-Square test was used to analyze the categorical data, and descriptive statistics were presented as frequency (%). The p-values below 0.05 were considered statistically significant.

Results

The study included a total of 127 children of which 63.8% (n = 81) were male. The children were divided into two groups according to the surgical procedure. The first group (AE, n = 73) included those with adenoidectomy; the second group (ATE, n = 54) included those with adenoidectomy and tonsillectomy. No significant difference was found between the two groups regarding the demographic data (p>0.05) (Table 2). The duration of the surgery was significantly shorter in AE (30 min) than ATE (52.5min). Mean fasting time and baseline hemodynamic measurements (SAP, DAP, MAP, and HR) were not significantly different between the groups (Table 2). In addition, the proportion of children over the age of 3 was not different between the two groups (93.2% in AE vs. 90.7% in ATE, p = 0.442).

Table 2. Demographic Data

|   | Group 1<br>(n=73 ) | Group 2<br>(n=54) | P     |
|---|--------------------|-------------------|-------|
| Sex n (%)   |                    |                   |       |
| Male  | 44 (60.3%)         | 37 (68.5%)        | 0.442 |
| Female  | 29 (39.7%)         | 17 (31.5%)        |       |
| Age (year) median (IQR)                                     | 5 (3.5)            | 6 (5)             | 0.335 |
| Weight (kg) median (IQR)                                    | 18 (11.2)          | 20 (17.5)         | 0.170 |
| Height median (IQR)   | 108 (21)           | 112 (32)          | 0.198 |
| Duration of the surgery (min.) median (IQR)                 | 30 (17.5)          | 52.5 (15)         | 0.001 |
| Total fluid (ml) median (IQR)                               | 150 (65)           | 180 (120)         | 0.166 |
| Fasting time (hour) median (IQR)                            | 9 (2)              | 9 (2)             | 0.435 |
| Basal SAP (mmHg) median (IQR)                               | 103(35)            | 109 (44)          | 0.263 |
| Basal DAP (mmHg) median (IQR)                               | 57(16)             | 52.5(17)          | 0.290 |
| Basal MAP (mmHg) median (IQR)                               | 75(15)             | 77(19)            | 0.253 |
| Basal HR (bpm) median (IQR)                                 | 116(17)            | 119.5(20)         | 0.149 |
| Neutrophil median (10 <sup>5</sup> /mm <sup>3</sup> ) (IQR) | 4.794 (3.170)      | 4.015 (1.935)     | 0.007 |
| lymphocyte (10 <sup>5</sup> /mm <sup>3</sup> ) median (IQR) | 3.600 (1.436)      | 3.130 (1.778)     | 0.106 |
| Platelet (10 <sup>5</sup> /mm <sup>3</sup> ) median (IQR)   | 348 (110)          | 328 (75)          | 0.03  |
| NLR median (IQR)  | 1.31 (0.68)        | 1.08 (0.96)       | 0.337 |
| PLR median (IQR)  | 97.96 (42.65)      | 103.70 (41.36)    | 0.334 |

IQR: interquartile range, SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure, HR: heart rate, NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

The rate of vomiting at any time post-surgery was 23.6% (n = 30). No significant difference was found between the groups regarding the rate of vomiting (19.2% vs. 29.6%) (p = 0.246). Among all children, only 5 (3.9%) required antiemetic treatment due to vomiting; no significant difference was found between the groups regarding antiemetic use (p = 0.907). At minute 1 in PACU, grade-1 PONV (mild nausea/vomit not requiring meto-

clopramide treatment), grade-2 PONV (nausea/vomit requiring metoclopramide treatment), and grade-3 PONV (severe nausea/vomit resistant to metoclopramide treatment) were 8.2%, 0%, and 1.4% in AE and 16.7%, 3.7%, and 0% in ATE, respectively. At minute 15 in PACU, only grade-1 PONV was present in both AE and ATE groups with no significant difference between the groups (13.7% and 16.7%, respectively). At minute 30 in PACU, only grade-1 PONV was present in AE group (4.1%) while grade-2 PONV was present in ATE group (1.9%). No PONV was observed at the 1st, 4th, and 6th-hour evaluations during the inpatient stay. In PACU, 79.5% of the children had no complications; agitation (n = 10), bronchospasm (n = 10), and sore throat (n = 6) were observed in the rest.

The CHEOPS score was 8 or above at any time in 18.9% (n = 24) of all children; no significant difference was found between the two groups (p = 0.493). In addition, no significant difference was found between the two groups regarding the CHEOPS scores at postoperative 1st, 15th, or 30th minute in PACU, and postoperative 1st, 4th, or 6th hour (p> 0.05) during the inpatient stay (Figure 3).

No significant difference was found between the hemodynamic parameters (SAP, DAP, MAP, and HR) measured during surgery (p> 0.05).

In the whole patient group, median neutrophil count was 4.480 (IQR:2.500) ×103/mm3, median lymphocyte count was 3.402 (IQR: 1.651) × 103/mm3, and median platelet value was 337 (IQR:97)×103/mm3. Neutrophil and platelet counts in the AE group were significantly lower than those in the ATE group, but no difference was found between lymphocyte counts (Table 2). Median NLR and PLR were 1.31 and 97.96 in the AE group, which were 1.08 and 103.70 in the ATE group, respectively. No difference was found between the two groups regarding the NLR and PLR (Table 1, Figure 1, Figure 2). Furthermore, no correlation was found between preoperative NLR or PLR and the PONV or CHEOPS scores in all children (p> 0.05).

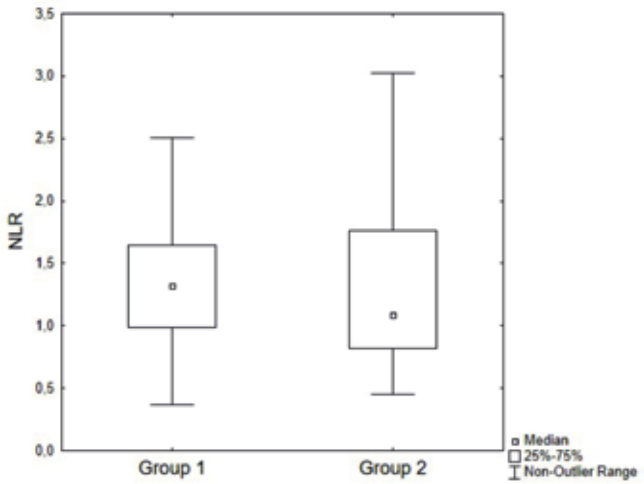


Figure 1. Comparison of NLR of the two groups.

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between preoperative NLR or PLR and postoperative nausea/vomiting (PONV) or postoperative pain (POP) in children undergoing adenoidectomy and adenotonsillectomy. In this study, we found that preoperative NLR and PLR

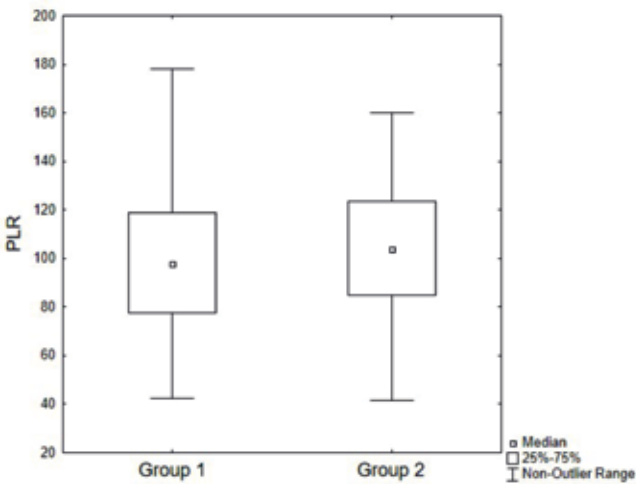


Figure 2. Comparison of PLR of the two groups.

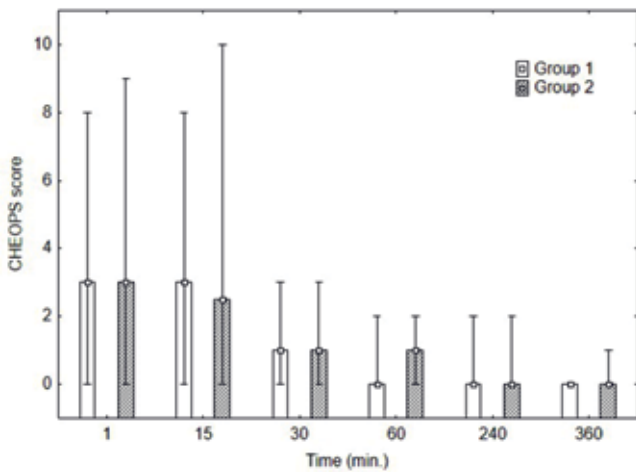


Figure 3. Variation of the CHEOPS scores of the two groups over time.

were similar in children who underwent AE or ATE. In addition, we did not find any relationship between preoperative NLR or PLR and the PONV or POP.

In the literature, the incidence of PONV among children who underwent AE or ATE has been reported as 25-30% [3]. The prevalence of PONV among all children in this study (23.6%) was slightly lower than that in previous studies. However, it was found that there was no difference between the groups regarding the frequency of vomiting and antiemetic use. In addition, no relationship was found between the NLR or PLR values, which were determined in the absence of active infections, and the PONV in children who underwent AE or ATE in our study.

There are four known risk factors related to PONV: duration of surgery > 30 min, age >3 years, history of PONV, and strabismus surgery [14]. In our study, the duration of surgery in the ATE group (52.5 min) was significantly longer than that in the AE group (30 min). Although the incidence of vomiting in the ATE group (29.6%) was higher than that in the AE group (19.6%), the difference was not statistically significant. The other risk factors for PONV were the same in both groups. For this reason, we believe that we have found a lower incidence of vomiting in our study compared to the previous studies.

It is known that the most common causes of infection among children are upper respiratory tract infections (URTIs). Although lymphoid tissue is actively involved in the fight against micro-

organisms during infection, adenoid and tonsillar tissues might be a breeding ground for viruses and bacteria [15]. As a result, recurrent URTI leads to adenoid and tonsil hypertrophy.

Neutrophils and lymphocytes are primary cells that have an important role in the body's defense system against infections [7]. Increased levels of neutrophils and decreased lymphocytes should alert the clinician to infection. The NLR and PLR are considered novel clinical indicators of systemic inflammation and used in the clinic for the diagnosis of various diseases [9-10, 16-18]. The increase in NLR and PLR, which are easily calculated from hematological evaluations, is known to be related to the severity of inflammation in particular. However, the cut-off values of these new markers in the definition of active inflammation in children are still unknown [19]. In a prospective study of familial Mediterranean fever (FMF), an autoinflammatory disease, the NLR has been reported to strongly correlate with other acute inflammation markers (C reactive protein, serum amyloid A) during the most severe period of episodes and inflammation [16, 20]. However, in the absence of FMF episodes (i.e. during the period of subclinical inflammation), the NLR has been found insufficient to define inflammation [16]. Since we did not have a control group in our study, we could not compare the NLR and PLR in this study with those in healthy children.

Some studies have reported the NLR cut off for active infection to be  $\geq 2$  [4, 20-21]. However, to authors' knowledge, no cut-off value has been reported for the NLR and PLR as an indication of active infection in children. In a study of 498 children, the best cut-off value for the NLR was reported to be 1.13 [22]. In our study, mean NLR of the children (without active infection) in the AE (NLR = 1.31) and ATE group (NLR = 1.08) were found to be lower than those in the other studies in the literature. In a study, preoperative NLR rates in children with chronic tonsillitis (1.98) were significantly higher than those in children with adenotonsillar hypertrophy (1.35) or adenoid hypertrophy (1.23) [23]. The children with chronic tonsillitis were not included since the number of such patients (n = 6) was low in our study, which we thought might have affected our results.

The differences in the NLR and PLR among children in different studies might be related to the difference in patient diagnoses and number of cases evaluated in these studies. In a study involving children with otitis media, mean NLR and PLR were found to be 1.6 and 102 in the study group including patients with mucous otitis media and 1.1 and 91.7 in the control group including patients with serous otitis media, respectively [11]. In another study, mean NLR in patients with FMF during the episodes and during attack-free periods and in the control group were  $2.88 \pm 2.9$ ,  $1.68 \pm 1.86$ , and  $1.59 \pm 0.66$ , respectively. Mean PLR in these groups were  $142.6 \pm 70.3$ ,  $122 \pm 57.9$ , and  $87.1 \pm 31.1$ , respectively [17]. These values were significantly higher than the values in our study. Thus, we think that there may be several reasons for lower preoperative NLR or PLR in children.

To our knowledge, the relationship between preoperative NLR or PLR and the complications of surgical procedures were not investigated previously. Previous studies in children focused on infectious, autoinflammatory, cardiac and oncological diseases [7,11,17,22]. A previous study involving adult patients reported that preoperative NLR was associated with PONV. However, we think the fact that the total number of cases (n = 64) in that

study was lower and the incidence of vomiting (43.8%) was higher than in our study has influenced the results [4]. We had expected that we would find higher NLR and PLR due to hypersensitivity in children who underwent AE and due to chronic infection in children who underwent ATE. However, no relationship was found between the preoperative NLR or PLR and PONV or POP in our prospective study. Therefore, pre-operative NLR and PLR in children undergoing AE or ATE could be low since there was no active infection. In addition, these novel parameters may not be effective in detecting subclinical infection as indicated in the previous studies [17].

### Limitations

The most important limitation of our study was the low number of cases. To our knowledge, no previous study has investigated the preoperative NLR or PLR in children undergoing AE or ATE and PONV or POP. There is a need for studies involving a large number of cases in order to elucidate this matter. In addition, the patients who underwent tonsillectomy were not included in the study since the number of these cases was low ( $n = 6$ ). Evaluation of this group of patients might have influenced the results. Thirdly, our study did not include a control group; therefore, we could not comment on how preoperative NLR and PLR of the operated children were compared to those of healthy children. Finally, we did not investigate the relationship between the NLR or PLR and the CRP, one of the acute-phase reactants.

### Conclusion

Preoperative NLR and PLR may not be effective in predicting PONV or POP in children undergoing adenoidectomy or adenotonsillectomy. Studies involving a large number of cases are needed to elucidate this matter.

### Scientific Responsibility Statement

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

### Animal and human rights statement

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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### Conflict of interest

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